ANNEX 2

UTMB The University of Texas Medical Branch

Department of Human Biological Chemistry & Genetics

CELL BIOLOGY

Nicole E. Murray

Assistant Professor

Affiliations: Department of Human Biological Chemistry & Genetics; Scientist, Sealy Center for Cancer Cell Biology

Telephone: (409) 747-1935
Fax: (409) 747-1938
E-mail: **nmurray@utmb.edu**
Campus Location: 9.162 Medical Research Building
Mail Route: 1048

Link

Sealy Center for Cancer Cell Biology Personnel Webpage

Education

B.A. 1989 Case Western Reserve University

Ph.D. 1995 Case Western Reserve University

Research Interests

Colon cancer results from progressive loss of regulation of the normal growth inhibitory, differentiation and apoptotic signals in colonic epithelial cells. Our long-term goal is to understand the role of protein kinase C (PKC) isozymes in colonic epithelial cell biology and colon carcinogenesis. Using an *in vivo* transgenic mouse model system, we have recently demonstrated a direct role for PKCbII in colonic epithelial cell proliferation and colon carcinogenesis. We are currently investigating the interaction of dietary fat and colonic PKCbII function in

susceptibility to colon carcinogenesis.

Several lines of evidence suggest that the atypical PKC iota isoform (PKCi) also plays an important promotive role in colon carcinogenesis. First, PKCi expression is elevated in colon tumors relative to uninvolved colonic epithelium. Second, expression of PKCi protects cancer cells from apoptosis by activating NF-kB. Third, PKCi plays a requisite role in the transformation of intestinal epithelial cells by activated Ras, an oncogene commonly mutated in colon cancer. Take together these data indicate that PKCi plays a key role in colon carcinogenesis by enhancing cell survival. We hypothesize that PKCi protects colonic epithelial cells against apoptosis and that elevated PKCi in the colonic epithelium will result in an increased susceptibility to colon carcinogenesis. We have generated transgenic mice that express constitutively active (ca) or dominant-negative (dn) mutant forms of PKCi in the colonic epithelium. In preliminary studies, we have detected a decrease in basal apoptosis of the colonic epithelium in mice expressing caPKCi and a corresponding increase in susceptibility to formation of early preneoplastic lesions. Future studies will investigate the role of PKCi in colonic epithelial cell homeostasis and susceptibility to colon carcinogenesis by further characterizing our caPKCi and dnPKCi transgenic mice. In addition, we will assess the role of PKCi in mediating the effects of K-ras on colonic epithelial cell homeostasis, colon carcinogenesis and NF-kB signaling in-vivo.

Selected Publications

Murray, N.R., Thompson, L.J. and Fields, A.P. The Role of Protein Kinase C in Cellular Proliferation and Cell Cycle Control. In: *Protein Kinase C*, P.J. Parker and L.V. Dekker, eds., R.G. Landes Press, pp. 97-120, 1997.

Murray, N.R. and Fields, A.P. Atypical Protein Kinase C i Protects Human Leukemia Cells Against Drug-induced Apoptosis. *J. Biol. Chem.* 272, 27525-27528, 1997.

Murray, N.R. and Fields, A.P. Phosphatidylglycerol is a Physiologic Activator of Nuclear Protein Kinase C. *J. Biol. Chem.* 273, 11514-11520, 1998.

Murray, N.R., Davidson, L.A., Chapkin, R.S., Gustafson, W.C., Schattenberg, D.G. and Fields, A.P. Overexpression of Protein Kinase C b_{II} Induces Colonic Hyperproliferation and Increased Sensitivity to Colon Carcinogenesis. *J. Cell Biol.* 145:699-711, 1999.

Gokmen-Polar, Y., Murray, N.R., Velasco, M.A., Gatalica, Z. and Fields, A.P. Elevated protein kinase C b_{II} is an early promotive event in colon carcinogenesis. *Cancer Research*, 61:1375-1381, 2001.